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KEYNOTE LECTURE

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Molecular imaging: what can be used today

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Abstract

Biochemical cellular targets and more general metabolic processes in cancer cells can be visualised. Extensive data are available on molecular imaging in preclinical models. However, innovative tracers move slowly to the clinic. This review provides information on the currently available methods of metabolic imaging, especially using PET in humans. The uptake mechanisms of tracer methods and a brief discussion of the more 'molecular' targeted methods are presented. The main focus is on the different classes of tracers and their application in various types of cancer within each class of tracers, based on the current literature and our own experience. Studies with [¹⁸F]FDG (energy metabolism), radiolabelled amino acids (protein metabolism), [¹⁸F]FLT (DNA metabolism), [¹¹C]choline (cell membrane metabolism) as general metabolic tracer methods and [¹⁸F]DOPA (biogenic amine metabolism) as a more specific tracer method are discussed. As an example, molecular imaging methods that target the HER2 receptor and somatostatin receptor are described.

Keywords: *Molecular imaging; oncology.*

Introduction

Several modalities can be used in humans for molecular imaging, such as single photon emission computed tomography (SPECT), positron emission tomography (PET), magnetic resonance imaging (MRI) and computed tomography (CT). The combination of the increasing availability of PET and conventional nuclear medicine imaging methods fused with CT/MRI for precise anatomical localisation, the discovery of a multitude of new targets, and rationally designed drugs in oncology, have led to a tremendous interest in molecular imaging in oncology. Nuclear medicine imaging methods use tracers that target specific mechanisms in cancer cells and tissues. Depending on the properties of the tracers, various aspects of cancer cells can be targeted and visualised. These methods can be used in staging and restaging of cancer patients, evaluation and prediction of treatment response, and may contribute to the determination of the prognosis of patients. Also in the characterisation of lesions, the domain of pathological

evaluation, imaging methods may contribute to oncology, as they permit total body imaging in a non-invasive way. The new anti-cancer drugs, consisting of both small (e.g. tyrosine kinase inhibitors) or large molecules (e.g. monoclonal antibodies), can often be radiolabelled and molecular imaging methods may generate information on biodistribution, metabolism and treatment induced changes in the targets of these drugs. The process of developing specific tracers, however, is laborious and, after radiochemical production, extensive evaluation is required before they can be used clinically.

Apart from the increasing interest in specific biochemical targets, currently available molecular imaging methods target more general metabolic processes in cancer cells. Among all the targets for imaging that are theoretically present during oncogenesis, imaging of metabolic targets is generally called 'metabolic imaging', whereas methods aimed at more specific biochemical targets could be regarded as 'molecular imaging'. However, the precise definition of these terms is rather subjective.

The general principles of nuclear medicine imaging also apply to molecular imaging. These include knowledge of the normal distribution of a tumour tracer that determines in what regions of the body the method may be successful. For example, high background uptake in an organ may interfere with tumour visualisation in that organ. Another main factor is the level of uptake. Visualisation depends on the detecting system (PET camera, gamma camera), but also strongly on the amount of tracer that is present at or in the target. In theory, a sub-millimetre lesion can be detected, as long as tracer uptake is high enough. On the other hand, a large lesion may be missed when the uptake level is too low. In contrast with radiological methods, it is therefore in principle not possible to determine a detection threshold, although in daily practice this threshold is generally around 0.5–1 cm for the best methods.

Extensive data are available on molecular imaging in preclinical models. The main aim of this review is to provide information on the currently available methods for metabolic imaging, especially with regard to PET in humans. A special focus is placed on the uptake mechanisms of tracer methods, as this is critical in understanding the images. Finally, a brief discussion of the more ‘molecular’ targeted methods is presented. The main focus is on the different classes of tracers, describing applications in various types of cancer within each class of tracers, based on the current literature and our own experience. We discuss [^{18}F]fluorodeoxyglucose ([^{18}F]FDG, energy metabolism), radiolabelled amino acids (protein metabolism), [^{18}F]fluorothymidine ([^{18}F]FLT, DNA metabolism), [^{11}C]choline (cell membrane metabolism) as general metabolic tracer methods, and [^{18}F]DOPA (biogenic amine metabolism) as a more specific tracer method. As an example of molecular imaging, we describe methods that target the HER2 receptor.

[^{18}F]FDG: energy metabolism

It has long been known that tumours contain large quantities of lactic acid, because they rely on anaerobic glycolysis for a major part of their energy consumption^[1]. This is a relatively inefficient process, since anaerobic glycolysis generates only a limited amount of energy (ATP) per molecule of glucose. This inefficient use of ‘fuel’ results in a strongly increased demand for glucose in cancer cells. Generally, tumour cells have upregulated all the mechanisms that are necessary to obtain glucose, such as the GLUT1 transmembrane transporter and intracellular enzymes such as hexokinase^[2]. This is the uptake principle of the [^{18}F]FDG tracer that is a direct analogue of glucose. The strongly increased uptake of FDG in cancer cells contrasts with most normal cells and organs. In addition, once FDG has entered the cell, it is phosphorylated but, unlike glucose itself, it is not further metabolised. This intracellular trapping, in combination

with the relatively high resolution of PET cameras, leads to adequate detection properties of tumours and metastases, provided they are metabolically active.

Normal distribution of FDG includes high uptake in the brain, especially in the grey matter, and in the kidneys and bladder, because of renal clearance. Moderate background uptake is generally present in the liver, muscles, small intestine and bone marrow, but this background uptake is (sufficiently) low to permit visualisation of tumour lesions.

Many clinical applications have emerged over recent years and because of the rapidly expanding availability of this technique, the list is growing steadily. Among the widely accepted indications are staging and/or restaging of non-small cell lung cancer^[3], malignant lymphoma, head-and-neck cancer, colorectal cancer, oesophageal cancer^[4], melanoma, and thyroid cancer. In each type of cancer the precise role of [^{18}F]FDG PET depends on the properties of the tumour and the possibilities of other diagnostic modalities. Recently, the Food and Drug Administration in the USA has generalised the accepted indications for PET, instead of the detailed list of separate indications that existed before^[5]. [^{18}F]FDG PET is now approved ‘for assessment of abnormal glucose metabolism to assist in the evaluation of malignancy in patients with known or suspected abnormalities found by other testing modalities, or in patients with an existing diagnosis of cancer’^[5].

[^{18}F]FDG PET can be of interest to follow the effects of new types of treatment. The best example of this application is response evaluation of the signal transduction inhibitor imatinib (Glivec). This biochemically engineered drug appears to shut down the energy metabolism in gastro-intestinal stroma cell tumours, almost immediately after the start of treatment. While morphological imaging does not show changes, [^{18}F]FDG PET demonstrates a dramatic decrease in metabolic rate, which appears helpful in the early identification of responders^[6,7]. The EORTC-PET Group has established response assessment guidelines for PET^[8]. A major new development in molecular imaging is the development of image fusion methods, such as PET-CT scanners or PET-CT/MRI fusing software. These new methods combine the precise anatomical information of CT/MRI with the metabolic information from PET. In this way, accurate localisation of PET lesions becomes possible and the interpretation of both PET and CT scans improves^[9]. In addition to PET-CT, simulator hardware integrated with innovative software for radiotherapy planning assisted by [^{18}F]FDG PET imaging is currently under study.

The drawbacks of FDG include uptake by inflammatory tissues and cells, which may interfere with oncological imaging^[10]. In general, positive PET findings require cytological or histological confirmation. In the assessment of brain tumours and metastases, [^{18}F]FDG PET is difficult because of high background

uptake. Finally, some tumours, such as low-grade sarcoma or prostate cancer, have a low uptake of FDG, which precludes successful imaging. For prostate cancer, the proximity of the bladder further interferes with imaging.

Radiolabelled amino acids: protein metabolism

Synthesis of proteins is a fundamental process for all cellular functions. Because of the uncontrolled and accelerated growth of cancer, the process of protein synthesis in tumours is increased. As a consequence, the demand for amino acids, the building blocks of proteins, is increased. Therefore, it is expected that radiolabelled amino acid tracers will also accumulate in tumours, and subsequent imaging of the amino acid metabolism could provide useful information with regard to tumour metabolism. Nearly all amino acids and slightly modified variants have been radiolabelled, but only a few have passed the prerequisites (reliable production, stability *in vivo*, adequate tumour uptake) to a degree sufficient for use clinically. Among these few are [^{11}C]methionine (MET), [^{11}C]tyrosine (TYR), [^{18}F]fluorethyl-tyrosine (FET) for PET imaging, and [^{123}I]iodomethyl-tyrosine (IMT) for SPECT imaging^[11].

To understand how cellular processes are actually represented on the images obtained after administration of amino acid tracers, extensive preclinical research has been performed. Protein metabolism can be divided into amino acid transport (from plasma into the cell) and protein synthesis (incorporation in protein). IMT uptake appears to represent the increased transport into tumour cells, TYR uptake represents both transport and protein synthesis, and MET uptake represents transport, but partly also protein synthesis and other cellular processes. It appears, however, that these differences do not translate into different clinical applicability. Amino acid imaging is less influenced by inflammation, which is advantageous in comparison with FDG PET imaging. However, also for amino acids, tumour specificity is not perfect^[12].

In brain tumour imaging, the use of radiolabelled amino acids is quite well established since [^{18}F]FDG PET does not perform well here. Applications include tumour grading, delineation, evaluation of treatment response, and recurrence detection. Diagnostic accuracy of amino acid imaging in brain tumours is adequate, and probably has advantageous diagnostic value. However, the true therapeutic value and value for the prediction of final patient outcome still needs to be established. In other tumours, such as head-and-neck or lung cancer, findings suggest reasonable diagnostic accuracy, but inferior diagnostic value in comparison with [^{18}F]FDG PET^[13]. In most other tumours, the data do not permit definitive conclusions yet, but the general feasibility of amino acid imaging has been sufficiently demonstrated.

In nearly all tumour types more research is required in larger patient series and in well-defined clinical settings.

[^{18}F]FLT: DNA metabolism

In recent years [^{18}F]FLT has attracted much attention, as the end result of a long search for a tracer, the uptake of which would accurately reflect DNA synthesis^[13]. This, in turn, would directly reflect the tumour proliferation status, which would be clinically helpful, for instance in response assessment. Theoretically FLT may be less dependent on interference from inflammatory cells, as compared to FDG. The uptake mechanism of FLT is now clear. FLT is transported across cell membranes by nucleoside transporter proteins. Once intracellular, FLT is phosphorylated by thymidine kinase I. Comparable to FDG, the phosphorylated tracer is trapped intracellularly, but is not further metabolised into DNA. It is important to realise that there are two main pathways involved in DNA synthesis. The exogenous or 'salvage' pathway, which utilises precursors from outside the cell that are phosphorylated by TK1, and the endogenous pathway, in which intracellular molecules, such as uridine monophosphate, enter DNA synthesis after phosphorylation by thymidylate synthase. The uptake of FLT appears to be a measure of the activity of the salvage pathway, and therefore depends on the activity of TK1. In general, TK1 is approximately 10-fold increased in cancer cells, especially during the S phase of the cell cycle^[14].

It has now been demonstrated in many types of cancer, that FLT uptake *in vivo* is a measure of tumour proliferation activity. In addition, in *in vitro* and animal studies comparing FDG and FLT have repeatedly confirmed that FLT uptake in inflammatory tissue is considerably less than FDG, which is advantageous. However, uptake in tumour tissue itself appears to be lower than FDG, as has been demonstrated in many types of cancer^[14]. Since high uptake is among the principle requirements of any successful imaging method (especially when applied in cancer staging), this is an important drawback. FLT PET, therefore, seems less suitable for staging of cancer, and currently most research focuses on response evaluation.

In FLT based response evaluation one has to keep in mind that FLT uptake is a measure of the salvage pathway of DNA synthesis. For example, cytostatic agents that effectively cause arrest of the cell cycle in the S-phase, such as 5-fluorouracil or methotrexate, lead to an increase in FLT uptake. Similarly, agents that block the endogenous pathway, such as gemcitabine, lead to overactivity of the salvage pathway, and with that, FLT uptake increases. Agents such as cisplatin or doxorubicin, however, inhibit both pathways and as a result decrease FLT uptake. These cellular effects have been demonstrated *in vitro* in cell cultures and may be temporary and different *in vivo*. Indeed, *in vivo* imaging in animals has demonstrated that FLT tumour uptake

declines rather rapidly (days to weeks), after various forms of anti-tumour treatment.

Therefore, [^{18}F]FLT PET imaging currently has no accepted clinical indication, but its attractive uptake mechanism, minor uptake in inflamed tissue and strong association with proliferation activity may lead to valuable applications in response-assessment^[15].

Choline based tracers: membrane metabolism

Choline is an important precursor in the synthesis of cell membranes. As choline can be radiolabelled simply with carbon-11, the idea of using [^{11}C]choline for imaging of cancer is obvious, since dividing cells require building blocks for membranes. Various tracers derived from choline have recently emerged and are currently being tested. The most used variant, [^{11}C]choline is chemically identical to choline. However, fluorine-18 variants also exist^[16].

The uptake of choline appears to be driven by the activity of choline kinase, which is generally increased in tumour cells. Choline is intracellularly phosphorylated and subsequently enters phospholipid synthesis pathways. High levels of choline and its metabolites have long been known from magnetic resonance spectroscopy imaging.

The normal appearance of a choline PET scan includes high uptake in the liver and minor uptake in bone marrow and intestinal tissues. The pancreas may also be visible, as pancreatic juice contains phosphatidyl cholines. An important advantage, compared to FDG, is the virtual absence of bladder activity, since choline is not cleared by the kidneys. Although choline can be considered a general tumour tracer, it appears to be taken up by prostate tissue in particular. The precise metabolic background is not fully clear, but this property, combined with the absence of bladder activity, has led to increasing application of choline PET imaging in prostate cancer staging and restaging, which is still notoriously difficult with the diagnostic methods currently available.

Choline uptake in prostate cancer is clearly higher than in normal and hypertrophic prostate tissue, although some overlap exists. Primary tumours can therefore be visualised, next to lymph node metastases^[17–19]. As application of this technique is still in its infancy, it is too early to define the precise role. It is evident that general uptake of choline in tumour lesions is lower than FDG in FDG-avid types of cancer, which requires a higher detection threshold^[19]. An important clinical problem is to find a substrate in the case of biochemical recurrence after previous radical treatment of prostate cancer. Current studies have demonstrated that choline PET is able to detect recurrence at PSA values around 5–10^[20]. To select patients for salvage radiotherapy, however, a lower PSA limit is required. Especially

in the field of prostate cancer imaging, an important contribution is expected from combined PET-CT, as the lower uptake of this tracer makes the separation of true lesions from background activity ('noise') difficult. CT can help in this regard.

Choline has also been applied in other types of cancer. In brain tumours, similar to FLT and amino acids, tumours can be visualised. In other types, such as lung cancer and oesophageal cancer, it has been demonstrated that choline PET is inferior to [^{18}F]FDG PET for staging purposes^[21].

Somatostatin receptor imaging and [^{18}F]DOPA

Standard imaging of neuroendocrine gastrointestinal tumours consists, among other diagnostics, of somatostatin SPECT scanning. This scan can visualise somatostatin receptors on the tumour cell membrane^[22].

Neuroendocrine tumours are also characterised by the ability to take up decarboxylate and accumulate amine precursors. Aromatic-5-amino acid decarboxylase is the key enzyme in this decarboxylation process and is involved in both serotonin and catecholamine synthesis. Other catecholamine synthesising enzymes have been shown to be present in carcinoid tumours. These findings have led to the use of [^{11}C]DOPA and [^{18}F]DOPA in relatively small studies for the detection of neuroendocrine tumours^[23–25]. We performed a study with whole body PET, after injection of 100–200 MBq [^{18}F]DOPA and oral pre-treatment with carbidopa in patients with neuroendocrine tumours. CT and somatostatin scanning were performed within a short interval of tracer injection, using standard methods. Endpoints were the number of patients with positive tracer uptake, positive body regions (number of body regions with positive tracer uptake and the number of individual lesions with positive tracer uptake). Image interpretation of PET was blinded from other imaging studies. For precise localisation PET-CT image fusion was carried out. Newly detected lesions on PET were validated using conventional methods when feasible. This ongoing study includes 36 patients (19 males and 17 females). The [^{18}F]DOPA PET scan was positive in 35 of 36 patients (sensitivity 97%), and detected a mean of 45 lesions per patient. CT was positive in 31 of 35 patients (sensitivity 88%), with a mean of 39 lesions detected per patient. Somatostatin scintigraphy was positive in 27 of 33 patients (sensitivity 82%) with 27 lesions detected per patient. The largest numbers of lesions were observed in the liver, with 1251 lesions for [^{18}F]DOPA, 999 for CT and 541 for the somatostatin scans. In the extrahepatic abdomen, we found 138/23/43, and in the pelvic region 54/20/10 lesions, for the three techniques, respectively. In 15 out of 26 patients, software fusion of [^{18}F]DOPA PET and CT was performed and led to a better localisation of lesions. [^{18}F]DOPA PET was clearly

superior to CT and somatostatin scintigraphy for staging of neuroendocrine tumours. In addition, software-based image fusion improved localisation of tumour lesions^[26].

These data suggest that [¹⁸F]DOPA PET scanning is superior to the somatostatin scan in neuroendocrine patients with regard to localisation of tumour lesions.

HER2 imaging

The combination of the antibody trastuzumab directed against the HER2 growth factor receptor and chemotherapy can induce remissions but also cardiac dysfunction in HER2-positive metastatic breast cancer. We evaluated whether radiolabelled trastuzumab scintigraphy can predict cardiotoxicity, tumour response, and identify tumour lesions^[27]. In an ongoing study, patients with HER2 positive metastatic breast cancer, suitable for trastuzumab and paclitaxel, underwent gamma camera imaging after injection of 150 MBq of [¹¹¹In]DTPA-trastuzumab, prior to and after four therapy cycles. In known tumour lesions (CT, ultrasound, X-ray, bone scan), the degree of [¹¹¹In]DTPA-trastuzumab tumour uptake was expressed as the tumour vs. background uptake intensity ratio (T/bg ratio), and as % injected dose index (tumour vs. total body (TB) counts). Seventeen patients have been enrolled. Variable tumour uptake was present in all patients after 5 and 7 days, starting from day 1. The T/bg ratio was 2.1 (1.4–3.5), 0.6% TB (0.1–5.5) at day 1 and 1.9 (1.3–9.3), 0.7% TB (0.2–5.5) at day 7 after injection. One or more lesions were visualised in each patient, although not all known lesions. Previously unknown lesions were found in seven patients. Liver metastases were difficult to visualise due to high liver uptake. One patient with pre-existing cardiac arrhythmias showed myocardial uptake. We showed that radiolabelled trastuzumab scintigraphy can identify HER2 positive lesions and may assist in identifying metastases and predicting response. Defining a predictive value for cardiotoxicity and tumour response requires more patients. This study continues to recruit. In the future, the precise role for HER2 imaging in patients regarding tumour detection and prediction of cardiotoxicity has to be established. It is also not yet clear whether labelling of the whole antibody trastuzumab for SPECT scanning or labelling of fragments of the antibody, such as the diabodies for PET imaging, will be preferable in the future^[28].

Conclusions

Molecular imaging of tumours is still in its infancy. The increasing elucidation of molecular determinants of cancer and the wealth of molecular targeted drugs that are coming into clinical oncological practice make molecular tumour imaging a great challenge for the future. The hope is that apart from tumour staging, it will be used increasingly for early response prediction.

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